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E- or *Z*-selective synthesis of trisubstituted (2-fluoroalkenyl)iodonium salts by the reaction of (2-fluoroalkenyl)iodonium ylides with aldehydes

Satoshi Shimobaba, Ryuhei Tahara, Shoji Hara *

Graduate School of Engineering, Hokkaido University, Sapporo 060-8628, Japan

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ABSTRACT

Trisubstituted (2-fluoroalkenyl)iodonium salts were prepared *E*- or *Z*-selectively by the reaction of (fluoroalkenyl)iodonium ylides generated from (fluoroalkenyl)iodonium salts with aldehydes.

1. Introduction

Alkenyliodonium salts have been used as a versatile reagent in organic synthesis and many methods have been reported for their synthesis [1]. However, the stereoselective synthesis of acyclic alkenyliodonium salts having a substituent on the same carbon as the iodine is difficult and only few precedent works have been reported for their synthesis [2]. Recently, Ochiai et al. succeeded in preparing the (*E*)-isomer of trisubstituted (fluoroalkenyl)iodonium salts stereoselectively by the addition of iodotoluene difluoride to the unsymmetrical internal alkynes [3]. However, their method cannot be applied to the synthesis of the corresponding (*Z*)-isomers. Recently, we succeeded in the stereoselective synthesis of (fluoroalkenyl)boranes using the unstable (2-fluoroalkenyl)iodonium ylides **2** generated from (2-fluoroalkenyl)iodonium salts **1** by the treatment with LDA [4]. As both (*E*)- and (*Z*)-(2-fluoroalkenyl)iodonium salts can be prepared stereoselectively, the methodology using **2** is considerably promising [5]. We report here the *E*- or *Z*-selective synthesis of trisubstituted (fluoroalkenyl)iodonium salts **3** by the reaction of **2** with aldehydes (Scheme 1).

2. Results and discussion

When a THF solution of (*Z*)-(2-fluoro-1-dodecyl)(phenyl)iodonium salt **1a** [6] was treated with LDA in the presence of benzaldehyde at −78 °C, a viscous liquid was obtained after a work-up procedure. The ^{1}H NMR spectra of the viscous liquid showed no vinylic proton, and the ^{19}F NMR spectra showed a singlet peak at −63 ppm. In NOE studies, 5.5–6.6% interaction was observed between allylic protons and a benzylic proton. From these observations, the product was determined to be (*Z*)-(3-fluoro-1-hydroxy-1-phenyltridec-2-en-2-yl)(phenyl)iodonium salt **3a**. On the other hand, when the (*E*)-isomer of (2-fluoro-1-alkenyl)iodonium salt **1b** [7] was used in the reaction with benzaldehyde, a product different from **3a** was obtained. In the ^{19}F NMR spectra of this product, a singlet peak appeared at −77 ppm, and in NOE studies, no interaction was observed between allylic protons and a benzylic proton. From these observations, the product obtained from **1b** was determined to be (*E*)-(3-fluoro-1-hydroxy-1-phenyltridec-2-en-2-yl)(tolyl)iodonium salt **3b** (Scheme 2). Therefore, the generated ylides **2a** and **2b** reacted with benzaldehyde to give (*E*)- and (*Z*)-trisubstituted (fluoroalkenyl)iodonium salts **3a** and 3**b**, respectively, without losing their original stereochemistry.

Both aromatic and aliphatic aldehydes can be used in the reaction, and various hydroxyalkyl groups can be introduced to the vinylic carbon of the (fluoroalkenyl)iodonium salts. Furthermore, multi-functionalized trisubstituted (fluoroalkenyl)iodonium salts (**3e**–**g**) can be prepared using functionalized (fluoroalkenyl)iodonium salts (**1c**–**e**) as the starting material (entries 5–7, Table 1).

3. Conclusion

The (2-fluoroalkenyl)iodonium ylide generated from 2-(fluoroalkenyl)iodonium salt was shown to be used for the

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* Corresponding author. Fax: +81 11 706 6556.
E-mail address: shara@eng.hokudai.ac.jp (S. Hara).

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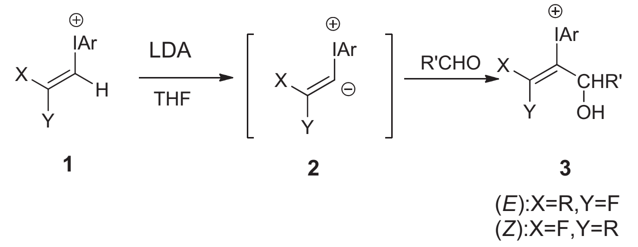


Scheme 1. The reaction of (2-fluoroalkenyl)iodonium ylide **2** with aldehyde.

synthesis of the trisubstituted (2-fluoroalkenyl)iodonium salt by the reaction with aldehyde. It was also shown that the reaction proceeds stereoselectively and from (*E*)- and (*Z*)-(2-fluoroalkenyl)iodonium salts, the corresponding (*E*)- and (*Z*)-trisubstituted (fluoroalkenyl)iodonium salts were formed without loss of the original stereochemistry. Introduction of functional group to the product was also performed.

4. Experimental

4.1. General

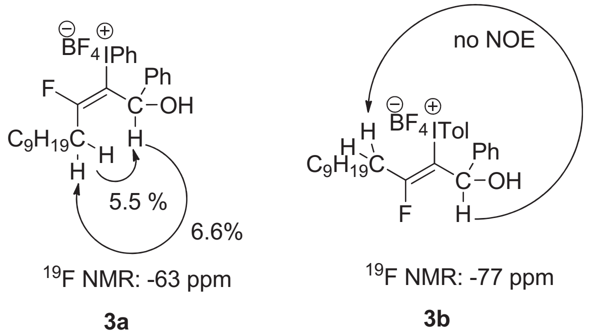
The IR spectra were recorded using a JASCO FT/IR-410. The ^{1}H NMR (400 MHz) spectra, ^{19}F NMR (376 MHz) spectra, and ^{13}C NMR (100 MHz) were recorded in CDCl$_3$ on a JEOL JNM-A400II FT NMR and the chemical shift, δ, is referred to TMS (^{1}H, ^{13}C) and CFCl$_3$ (^{19}F), respectively. The EI-high-resolution mass spectra were measured on a JEOL JMS-700TZ. *p*-Iodotoluene difluoride was prepared according to the literature [8]. 1-Alkynyliodonium salts were prepared from 1-alkyne according to the literature [9]. (*Z*)-(2-fluoro-1-alkenyl)iodonium salts (**1a, 1c**–**f**) were prepared from 1-alkynyliodonium salts according to the literature [6]. (*E*)-(2-fluoro-1-dodecyl)iodonium salt (**1b**) was prepared from 1-dodecyne and *p*-iodotoluene difluoride according to the literature [7].

4.2. General procedure for the reaction of **2** with aldehydes

To a THF solution (6 mL) of (2-fluoroalkenyl)iodonium salt **1** (0.5 mmol) and an aldehyde (0.7 mmol) was added a cooled THF solution (2 mL) of LDA (0.7 mmol) at −78 °C (for (*Z*)-isomer) or at −90 °C (for (*E*)-isomer), and the mixture was stirred at −60 °C for 1.5 h. After the addition of a 42% aqueous HBF$_4$ (2 mL), the cooling bath was removed and the mixture was stirred at room temperature for 1 h. Then, the product was extracted with ether (3× 10 mL) and the combined organic layer was dried over MgSO$_4$. After concentration under reduced pressure, the remained viscous liquid was washed with hexane. An upper hexane layer was removed by decantation (this operation was repeated twice). A volatile part was removed under high vacuum to give the (fluoroalkenyl)iodonium salt **3**.

4.2.1. (Z)-(3-fluoro-1-hydroxy-1-phenyl-2-tridecen-2-yl)(phenyl)iodonium tetrafluoroborate (*3a*)

Viscous liquid. IR (neat): 3484, 2925, 1656, 1060 cm^{-1}. ^{1}H NMR δ 0.88 (3H, t *J* = 7.2 Hz), 1.15–1.40 (14H, m), 1.50–1.80 (2H, m), 2.75–2.89 (2H, dt, *J* = 23.6, 7.8 Hz), 5.67 (1H, d, *J* = 3.3 Hz), 5.30–6.00 (1H, brs), 7.10–7.49 (10H, m). ^{13}C NMR δ 13.9, 22.5, 26.0, 28.9, 28.9, 29.1, 29.2, 29.3, 30.0 (d, $^{2}J_{C-F}$ = 24.8 Hz), 31.7, 69.2 (d $^{3}J_{C-F}$ = 3.5 Hz), 109.9, 112.2 (d, $^{2}J_{C-F}$ = 19.7 Hz) 125.6 (2C), 128.6, 128.8 (2C), 131.6 (2C), 132.3, 135.3 (2C), 138.6 (d, $^{4}J_{C-F}$ = 2.4 Hz), 168.1 (d, $^{1}J_{C-F}$ = 275.6 Hz). ^{19}F NMR δ −63.28 (1F, t, *J* = 22.9 Hz), −147.79 (s, 4F). HRMS (FAB, M^{+}−BF$_4$) calcd. for C$_{25}$H$_{33}$FOI 495.1560, found 495.1540.



Scheme 2. NOE study of (*Z*)- and (*E*)-trisubstituted (fluoroalkenyl)iodonium salts **3a** and **3b**.

4.2.2. (E)-(3-fluoro-1-hydroxy-1-phenyl-2-tridecen-2-yl)(p-tolyl)iodonium tetrafluoroborate (*3b*)

Viscous liquid. IR (neat) 3480, 2925, 1651, 1059 cm^{-1}. ^{1}H NMR (CDCl$_3$) δ 0.88 (3H, t, *J* = 6.9 Hz), 1.00–1.65 (16H, m), 2.29 (3H, s), 2.85–3.00 (2H, m), 4.60–4.90 (1H, s), 6.00 (1H, s), 6.90–7.50 (9H, m). ^{13}C NMR (CDCl$_3$) δ 14.0, 21.1, 22.6, 25.8, 28.9, 29.19, 29.2, 29.3, 29.4, 31.8, 33.9 (d $^{2}J_{C-F}$ = 24.4 Hz), 67.2 (d $^{3}J_{C-F}$ = 6.2 Hz), 106.5, 117.0 (d $^{2}J_{C-F}$ = 33.9 Hz), 125.7 (2C), 128.3, 128.9 (2C), 132.5 (2C), 134.9 (2C), 139.0, 143.4, 169.5 (d $^{1}J_{C-F}$ = 281.1 Hz). ^{19}F NMR (CDCl$_3$)δ −77.68 (1F, q, *J* = 18.0 Hz), −147.05 (4F). HRMS (FAB, M^{+}−BF$_4$) calcd. for C$_{26}$H$_{35}$FOI 509.1717, found 509.1711.

4.2.3. (Z)-(5-fluoro-3-hydroxy-2,2-dimethyl-4-pentadecen-4-yl)(phenyl)iodonium tetrafluoroborate (*3c*)

Viscous liquid. IR (neat) 3501, 2926, 1648, 1468, 1062 cm^{-1}. ^{1}H NMR δ 0.87 (3H, t, *J* = 7.0 Hz), 0.97 (9H, s), 1.20–1.70 (16H, m), 2.40–2.80 (2H, m), 4.17 (1H, s), 5.00–5.40 (1H, m), 7.40–8.00 (5H, m). ^{13}C NMR δ 14.0, 22.6, 25.4 (3C), 26.0, 29.0 (2C), 29.2 (2C), 29.4, 31.0, 31.1 (d, $^{2}J_{C-F}$ = 24.8 Hz), 31.8, 74.1, 108.1 (d, $^{2}J_{C-F}$ = 19.8 Hz), 110.8, 132.3 (2c), 132.7, 135.2 (2C), 168.5 (d, $^{1}J_{C-F}$ = 275.7 Hz). ^{19}F NMR δ −60.08 (1F, s), −148.31 (4F, s). HRMS (FAB, M^{+}−BF$_4$) calcd. for C$_{23}$H$_{37}$FOI 475.1873, found 475.1862.

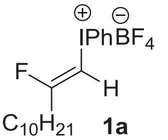
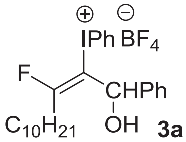
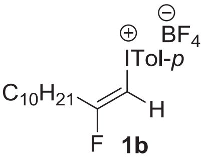
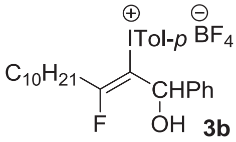
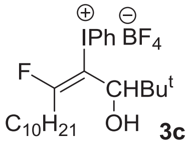
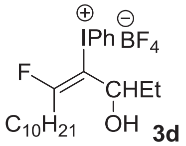
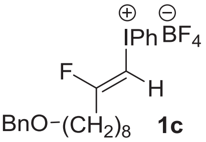
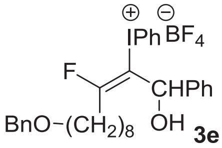
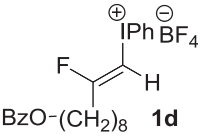
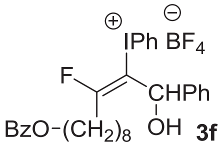
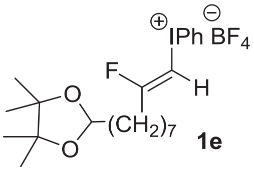
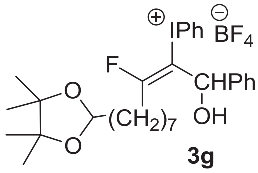
4.2.4. (Z)-(5-fluoro-3-hydroxy-4-pentadecen-4-yl)(phenyl)iodonium tetrafluoroborate (*3d*)

Viscous liquid. IR (neat) 3502, 2926, 1654, 1468, 1066 cm^{-1}. ^{1}H NMR δ 0.77 (3H, t, *J* = 7.5 Hz), 0.87 (3H, t, *J* = 7.2 Hz), 1.20–1.90 (18H, m), 2.50–2.80 (2H, m), 4.22–4.28 (1H, m), 4.85 (1H, brs), 7.40–8.05 (5H, m). ^{13}C NMR δ 9.5, 14.0, 22.6, 26.0, 28.9, 29.0, 29.2, 29.3, 29.4, 29.9, 30.4 (d, $^{2}J_{C-F}$ = 25.6 Hz), 31.8, 70.7 (d, $^{3}J_{C-F}$ = 2.4 Hz), 110.0, 111.2 (d, $^{2}J_{C-F}$ = 17.2 Hz), 132.3 (2C), 132.7, 135.8 (2C), 168.3 (d, $^{1}J_{C-F}$ = 275.9 Hz). ^{19}F NMR δ −61.41 (1F, t, *J* = 26.3 Hz), −147.45 (4F, s). HRMS (FAB, M^{+}−BF$_4$) calcd. for C$_{21}$H$_{33}$FOI 447.1560, found 447.1588.

4.2.5. (Z)-(11-benzyloxy-3-fluoro-1-hydroxy-1-phenyl-2-undecen-2-yl)(phenyl)iodonium tetrafluoroborate (*3e*)

Viscous liquid. IR (neat) 3482, 2932, 1541, 1060 cm^{-1}. ^{1}H NMR δ 1.20–1.80 (12H, m), 2.75–2.95 (2H, m), 3.44 (2H, t, *J* = 6.8 Hz), 4.47 (2H, s), 4.75–5.00 (1H, brs), 5.63 (1H, d, *J* = 3.4 Hz), 7.05–7.50 (15H, m). ^{13}C NMR δ 25.8, 25.9, 28.8 (2C), 29.0, 29.5, 30.0 (d, $^{2}J_{C-F}$ = 25.1 Hz), 69.1 (d, $^{3}J_{C-F}$ = 3.6 Hz), 70.3, 72.6, 110.0, 112.5 (d, $^{2}J_{C-F}$ = 20.1 Hz), 125.6 (2C), 127.4, 127.5 (2C), 128.2 (2C), 128.5, 128.7 (2C), 131.6 (2C), 132.2, 135.3 (2C), 138.4, 138.7 (d, $^{4}J_{C-F}$ = 1.92 Hz), 167.9 (d, $^{1}J_{C-F}$ = 277.8 Hz). ^{19}F NMR δ −63.69 (1F, t, *J* = 24.4 Hz), −148.07 (4F, s). HRMS (FAB, M^{+}−BF$_4$) calcd. for C$_{30}$H$_{35}$FO$_2$I 573.1660, found 573.1644.

Table 1
Reaction of (2-fluoroalkenyl)iodonium ylides **2** with aldehydes.

Entry	Iodonium salt **1**	Aldehyde	Product	Yield (%)[a]
1	 **1a**	PhCHO	 **3a**	85
2	 **1b**	PhCHO	 **3b**	(68)
3	**1a**	^{t}BuCHO	 **3c**	70
4	**1a**	EtCHO	 **3d**	79
5	 **1c**	PhCHO	 **3e**	75
6	 **1d**	PhCHO	 **3f**	83
7	 **1e**	PhCHO	 **3g**	(52)

[a] Isolated yield based on **1** used. In parentheses, ^{19}F NMR yield.

4.2.6. *(Z)-(11-benzoyloxy-3-fluoro-1-hydroxy-1-phenyl-2-undecen-2-yl)(phenyl)iodonium tetrafluoroborate (**3f**)*

Viscous liquid. IR (neat) 3478, 2934, 1714, 1284, cm^{-1}. ^{1}H NMR δ 1.05–1.85 (12H, m), 2.70–3.00 (2H, m), 4.27 (2H, t, $J = 6.6$ Hz), 5.69 (1H, s), 7.05–8.50 (15H, m). ^{13}C NMR δ 25.6, 25.9, 28.4, 28.7 (2C), 28.8, 30.0 (d, $^{2}J_{C-F} = 25.4$ Hz), 65.0, 69.2 (d, $^{3}J_{C-F} = 3.4$ Hz), 109.9, 112.5 (d, $^{2}J_{C-F} = 20.1$ Hz), 125.7 (2C), 128.2 (2C), 128.6, 128.8 (2C), 129.4 (2C), 130.1, 131.6 (2C), 132.3, 132.9, 135.4 (2C), 138.6, 166.8, 168.0 (d, $^{1}J_{C-F} = 277.8$ Hz). ^{19}F NMR δ −63.55 (1F, t, $J = 22.9$ Hz), −148.17 (4F). HRMS (FAB, $M^{+}-BF_4$) calcd. for $C_{30}H_{33}FO_3I$ 587.1453, found 587.1454.

4.2.7. *(Z)-{3-fluoro-1-hydroxy-1-phenyl-10-(4,4,5,5-tetramethyl-1,3-dioxolan-2-yl) dec-2-en-2-yl}(phenyl)iodonium tetrafluroborate (**3g**)*

Viscous liquid. IR (neat) 3480, 2979, 1651 cm^{-1}. ^{1}H NMR δ 1.19 (12H, s), 1.26–1.73 (12H, m), 2.72–2.97 (2H, m), 5.02 (1H, t, $J = 5.1$ Hz), 5.67 (1H, s), 7.17–7.47 (10H, m). ^{13}C NMR δ 21.7 (2C), 23.9 (2C), 24.0, 25.9, 28.6, 28.8, 29.0, 30.0 (d, $^{2}J_{C-F} = 25.0$ Hz), 36.0, 69.1 (d, $^{3}J_{C-F} = 3.1$ Hz), 81.7 (2C), 100.6, 110.0, 112.5 (d, $^{2}J_{C-F} = 19.3$ Hz), 125.63 (2C), 128.5, 128.8 (2C), 131.6 (2C), 132.3, 135.3 (2C), 138.6, 167.9 (d, $^{1}J_{C-F} = 276.1$ Hz). ^{19}F NMR δ −63.56 (1F, t, $J = 22.8$ Hz), −148.3 (4F, s). HRMS (FAB, $M^{+}-BF_4$) calcd. for $C_{29}H_{39}FO_3I$ 581.1922, found 581.1931.

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